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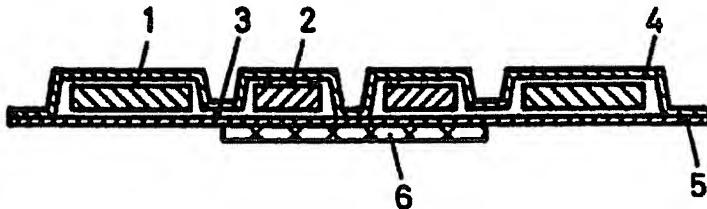
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(54) Title: CHILDPROOF BLISTER PACKAGE WITH DESSICANT

(57) Abstract

The blister package for moisture sensitive pharmaceutical preparations has cavities (1) for the effective substance comprising preparations and cavities (2) for drying agents, whereby each cavity (1) for effective substance comprising preparations by a canal is connected with a cavity (2) for drying agents and the cover sheet (5) in the region of the cavities (2) for drying agents is thus enforced by an additional protection sheet (6) so that a withdrawing of the drying agent is excluded if usual means are applied.



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## CHILDPROOF BLISTER PACKAGE WITH DESSICANT

Technical Field

5       The present invention regards a blister package, particularly a blister package providing preparation cavities and drying agent cavities for packaging moisture sensitive solid or semi-solid pharmaceutical preparations.

10       The expression blister package is used herein in its usual meaning, i.e. for any type of sheet package, preferably made of plastics and aluminum, which have cavities for the uptake of the solid to be packaged in the pan sheet (usually in the plastic sheet) and which  
15      are closed by sealing with a second sheet, a so called cover sheet, preferably a coated aluminum foil, whereby the product at its offtake can be pushed through the cover sheet by pressure on the pan sheet.

20       Background Art

Today, blister packages are a preferred packaging form for solid or semi-solid pharmaceutical preparations, respectively. They have the advantage that the preparations remain cleanly packed until they are used  
25      and furthermore - because of the usual labeling on the back side and/or on the top side - the risk of a mix-up is much reduced. Further advantages of the blister package are a reduced abrasion of the product, the possibility to get single units under retention of the primary  
30      package, water vapor resistance etc.

Today used blister packages have a certain water vapor permeability due to the plastic sheet making them unsuitable for the packaging of moisture sensitive products. The minimizing of the water vapor permeability  
35      by thickening the foil is only limitedly possible because of the technical practicability and the handling (pushing through).

Therefore, the moisture permeability with the today generally usual packages can only be improved by the material selection, i.e. as much as possible moisture impermeable laminate sheets. In this respect particularly 5 multilayer sheets have turned out to be suitable.

These known packages, however, are not suitable for very moisture sensitive preparations or for moderately moisture sensitive preparations destined for countries with humid-hot climate.

10 Several attempts have already been made to provide packages for the dry storage of pharmaceutical preparations.

A known procedure exclusively uses aluminum composite films as pan sheet and cover sheet. An additional drying effect can be achieved by providing two 15 cavities connected with each other for air exchange, from which one comprises a drying agent and the other one the pharmaceutical preparation. Such a package has the disadvantage that it is relatively expensive and that, particularly because of the lack of transparency, the risk 20 for the erroneous intake of the drying agent instead of the effective substance comprising preparation exists. Besides of the possibly occurring side effects of some 25 drying agents the non-consummation of the effective substance comprising preparation (pharmaceutical preparation) can very badly influence the state of health of the patient.

There have also already attempts been made to reduce the moisture intake of blister packages without 30 renouncing the transparency of the foil of at least one side of the package.

EP-A-0 466 068 describes a blister package in which each cavity for a pharmaceutical preparation is connected with a cavity for a drying agent. Additionally 35 a perforation can be provided enabling the separation of each combination of a pharmaceutical preparation and a drying agent.

The disadvantage of this blister package is that by accident the drying agent can easily be consumed, particularly with a separated unit.

FR-A-2 593 152 also describes a blister package with drying agent whereby several cavities for a pharmaceutical preparation are connected with one cavity for drying agents.

While for this package the risk of the accidental intake of the drying agent is reduced because of its exposed location and/or its largeness, this package bears the disadvantage that the drying effect is badly influenced if the pharmaceutical preparations are consumed in the wrong sequence.

FR-A-2 660 634 discloses a package comprising a drying agent whereby between the drying agent and the cover sheet a membrane is located to keep the drying agent at the desired place. The offtake of the charge is not performed by pushing the charge through the cover sheet but by peeling the cover sheet off. A peeling of the cover sheet from the drying agent is made more difficult by additional sealings.

Also known are children-resistant packages.

DE-OS-24 04 232 discloses a children-resistant package, however without any means to keep the pharmaceutical preparation dry. Besides of a removable tear resistant sheet on the cover sheet preventing pushing of the charge through the cover sheet, the cavities are thus formed, that a child cannot open them by biting on the blister.

US-5 172 812 discloses a children-resistant package with a rupturable cover sheet and with a paperboard material peelably laminated to the sheet of rupturable material. Furthermore a die cut is provided "misregistered" with the opening so that only a part of the paperboard material is peeled off from the opening so that the tablet can only be removed if pressure is ap-

plied in a specific manner. This document does not disclose a drying agent comprising package.

US-3 780 856 and US 3 835 995 both disclose blister packages with a cover sheet that is to be peeled off. In both packages a tear-off strip is provided where the cover sheet is not sealed to the carrier layer.

Short description of the invention

The problem of the present invention thus was  
10 to provide a blister package for the dry storage of pharmaceutical preparations, for which the accidental intake of the drying agent is prevented.

This problem is solved by a blister package with a pan sheet with preparation cavities and drying agent cavities as well as a cover sheet, characterized in that the blister package in the region of the drying agent cavities is reinforced thus, that the withdrawing of the charge with usual finger pressure is prevented, and that the reinforcement over the drying agent cavities  
20 cannot be removed by applying usual means. In the inventive blister package each cavity comprising a pharmaceutical preparation is connected to at least one cavity comprising a drying agent, and at least one sheet, particularly the cover sheet is reinforced in the region of  
25 the drying agent thus that the reinforcement over the drying agent cavities cannot be removed by usual application of usual means as for example pressing, pushing or peeling off with the fingers or the finger nails. By this package it is possible to secure the sufficiently dry  
30 storage of the tablets during the whole desired consummation period of the pharmaceutical preparation under consideration of the climatic situation and to simultaneously hinder the often even dangerous accidental intake of the drying agent. By not consuming the essential effective agent as well as by side effects of the drying agent the organism of a possibly already weakened patient  
35 may be further weakened.

Examples for an inventive blister package are shown in the Figures 1 to 6.

Short description of the drawings

5       Figure 1 is a top view on a blister package in which each pharmaceutical preparation cavity is connected to a drying agent cavity by a connecting passage, and with an additional protection sheet being placed on the cover sheet in the region of the drying agent,

10      Figure 2 is a section along the line II-II of the blister package of Figure 1,

      Figure 3 shows the structure of a specific protection sheet against withdrawing simultaneously serving as child-resistant,

15      Figure 4 is a top view on a blister package with a specific withdrawing-protection sheet according to Figure 3,

      Figure 5 is a section along line V-V of the blister package of Figure 4 during the peeling off of the  
20 protection sheet from the preparation side, and

      Figure 6 shows a blister package in which two preparation cavities are connected to one drying agent cavity.

25      Detailed description of the invention

      The inventive blister package has a pan sheet 4 with cavities 1 for the uptake of effective substance comprising preparations and cavities 2 for the uptake of drying agents as well as a cover sheet 5, characterized  
30 in that the blister package in the region of the drying agent cavities 2 is enforced thus, that the withdrawing of the charge with usual finger pressure is prevented, and that the reinforcement over the drying agent cavities 2 cannot be removed by applying usual means. Usually each  
35 cavity 1 is connected with at least one cavity 2 by a connecting means 3, thus that an air exchange is of course possible, but not a direct contact of the effec-

tive substance comprising preparation with the drying agent. Preferably said connecting means 3 is a connecting passage-like cavity in the formed pan sheet 4 of the blister package, which is particularly a plastic sheet.

5 The lifetime of the package can be controlled by the amount of drying agent used, dependent on the environmental conditions.

10 The amount of drying agent results from its water absorbing capacity, the blister design, the used foil quality, the provided storage conditions and the desired shelf life of the product.

15 For space reasons it can be advantageous if more than one cavity 1 for a pharmaceutical preparation is connected with one cavity 2 for a drying agent (e.g. as represented in Figure 6). Since the drying agent advantageously is also applied in the form of tablets whereby the dosage as well as the introduction into the cavities 2 is facilitated and additionally a clogging up of the passages by loose particles is diminished or 20 avoided, respectively, for such an embodiment possibly larger drying agent tablets are used.

25 Suitable as drying agent are all solid, preferably pharmaceutically harmless substances such as molecular sieves and silica gel. Considered as essential thereby is that the package comprises additional security elements preventing the accidental intake of the drying agent instead of the effective substance comprising preparation. Such a security measure can for example be the sealing of an additional plastic sheet in the drying 30 agent region, particularly onto the cover sheet 5. This additional sheet prevents a pushing through of the drying agent through the cover sheet 5. Preferably one additional sheet simultaneously covers several drying agent comprising cavities 2, resulting in an improved adhesion 35 thereof. This foil can be clear or colored. Measures on the side of the pan sheet 4 such as local coloring, local reinforcement of the sheet or covering hood, respec-

tively, etc. are possible but technically much more expansive.

Particularly if an additional protection sheet 6 shall simultaneously cover several drying agent cavities 2, it is preferred that the drying agent cavities 2 are situated adjacently, particularly in one or several adjacent rows.

The preferred inventive blister packages with enhanced security against withdrawing of the drying agents provide on the cover sheet side at least in the region of the cavities 2 for the uptake of drying agent a protection sheet 6.

The protection sheet 6 can be of any shape, provided that the withdrawing of the drying agent is effectively prevented. Suitable are e.g. plastic foils which, due to their toughness prohibit a pushing through. Because of their toughness polyethylene (PE) sheets or polyethylene composite films, respectively, for example a laminate of polyethylene (PE) and polyethyleneterephthalate (PET) sheet (PET/PE sheet) are preferred.

Also suitable are cover sheets 5 of a multi-layer laminate with the protection sheet 6 being already comprised (cf. Fig. 3). For example such sheets, which are commercially available, inside (contact to the pan sheet 4) have a hot-melt layer, e.g. a thermoplastic lacquer. As further layers an aluminum foil, an adhesive, a polyester sheet, e.g. polyethyleneterephthalate (PET), an adhesion enhancer, e.g. another solid adhesive layer, a paper layer and possibly an imprint follow. A sheet with e.g. 20 µm thickness of the Al-layer and 12 µm thickness of the polyester sheet and an adhesive with restricted adhesion in the laminate is e.g. available from Neher, Kreuzlingen, Switzerland, under the name Peel-Push foil.

The adhesive can either be thus construed that it only provides restricted laminate adhesion so that a separation between the cover sheet 5 and the protection sheet 6 is possible by hand, or it is thus that

the adhesion of the laminate is so strong that the multi-layer laminate is peeled off as such, i.e. cover sheet 5 and protection sheet 6 together.

When such a multilayer laminate with restricted laminate adhesion is used, the whole cover sheet region is covered, that is also the preparation region. Such a cover is considered as child-resistant. A usual pressing through of the tablet through the laminate is not possible.

For the inventive blister package it must be secured that the protection sheet part of the multilayer laminate can only be peeled off from the effective substance comprising preparations but not from the drying agent.

This is for example secured in that (as shown in Figures 4 and 5) in the effective substance comprising preparation part opening aids are provided, e.g. seal free zones 7, as well as a perforation or a cross section 8 to the drying agent region. By the perforation or the cross section 8, respectively, it is secured that, starting from the seal free zone 7, the protection sheet part of the multilayer laminate is only peeled off in the region of the effective substance comprising preparations. The seal free zones 7 are preferably located directly at the perforation or the cross section 8, or at the intersection of the perforation or the cross section 8 and the perforation or the cross section 9, so that the peel off direction necessarily leads away from the drying agent. The seal free zone 7 is e.g. made in that the sealing tool, e.g. a stamp, provides respective "cold" parts, and/or by deep drawing of the package form in the respective region, so that no contact can be made and at the same time the seizing of the loose sheet part is facilitated, or by punching out the respective zone from the pan sheet prior to sealing it with the cover sheet. Advantageously also between two pharmaceutical preparation cavities and/or between two drying agent cavities a per-

foration or cross section 9, respectively, is provided. The perforation or the cross section 8, respectively, as well as the perforation or cross section 9 preferably concern at least the protection foil part of the multi-layer laminate. Particularly a perforation 9 through the whole blister package can be provided so that single units can be separated. Since the drying agent region because of the protection foil is secured against withdrawing also for a 1:1 combination (one effective substance comprising preparation per drying agent tablet) no risk of withdrawing exists.

Important, however, is that the paper + PET complex can only be peeled off from the region of the preparation. This is achieved in that the opening aids 7 are exclusively present in the preparation field. If a sheet with an adhesive providing strong laminate adhesion between cover sheet 5 and protection sheet 6 is used, a perforation or cross section 8 as well as a perforation or cross section 9 must be provided to ensure that the multilayer laminate is only peeled off from one effective substance preparation, which then is laid open.

As a further protection measure, particularly with the multilayer laminate, the paper layer, particularly in the region over the drying agent, can be colored or provided with a warning imprint. Advantageous is also a label in the product region, e.g. specification of the weekdays etc., on which the respective tablet shall be consumed. Such a label additionally diminishes the probability that the sequence of the intake is thus that - e.g. for packages with several units for which one unit comprises more than one preparation cavity 1 per drying agent cavity 2 - all but one tablet of one unit are consumed at the beginning of the consumption, the one remaining tablet, however, is consumed as the last one of all units, so that the drying agent - because of the enhanced humidity access through the ruptured area of the

cover sheet 6 over the tablet cavities 1 - is extremely strained.

Furthermore, with the package a monitoring device can be provided indicating the complete consumption of the drying agent or the enhancement of the humidity, respectively. Known in this respect is e.g. the silica gel with indicator, a silica gel colored with  $\text{CoCl}_2$  to show the water absorption. Because of the side effects that may occur with the intake of  $\text{CoCl}_2$ , silica gel with indicator preferably should only be used in inventive blister packages providing the additional protection to prevent the intake of the drying agent.

The pan sheet itself should - as already mentioned above - be as little moisture permeable as possible. Furthermore it should be sealable as well as also having a good compatibility with the product. A today usual sheet for such applications is a combination sheet of PVC (polyvinylchloride), PE (polyethylene) and PVDC (polyvinylidenechloride). Such a sheet is e.g. sold under the name Alfoil®, Tristar®, Aclar®, etc. and extensively used for pharmaceuticals.

Also as cover sheet a usual sheet can be used, particularly one comprising an aluminium layer or an aluminium foil such as a usually used polymer coated aluminium foil or the above mentioned multilayer laminate, respectively.

The pan sheet is formed according to the blister design with usual methods and after the introduction of the drying agent and the product connected with the cover foil in a manner usual for blister packages, particularly sealed.

Example 1: Protection against withdrawing for blister packages

Onto the cover sheet, a usual aluminum sheet, in the region of the part to be protected against withdrawing (drying agent region) a protection sheet of

PET/PE (thickness about 60 µm) is sealed at about 120-130°C. Due to the toughness of the PET/PE sheet a pushing through of the drying agent is not possible. The thus secured blister package then can be perforated as desired,  
5 preferably between each unit.

Example 2: Protection against withdrawing by  
a multilayer laminate

10 The filled pan sheet is sealed at about 200°C with a multilayer laminate (Peel-Push-Folie from Neher, Kreuzlingen, Switzerland) according to Figure 3 as cover sheet and protection sheet instead of an aluminum sheet thus, that, in the product region at the perforation line  
15 to the drying agent region and at the perforation line between the units, for each unit at least one seal free zone is formed. If the seal is made by a stamp, this is achieved by "cold" zones on the stamp itself.

Then a perforation is made between the preparation cavities and the drying agent cavities.  
20

The withdrawing of the product is made in several steps:

- optionally separation of the blister yard along the perforation lines  
25 - peeling off of the outside cover sheet layers, here paper + PET-complex, at the seal free corners  
- pressing through of the product through the aluminum-foil fixed at the lower part by heat-sealing.

In that the seal free zones are situated at  
30 the border line between the drying agent region and the product region, so that the peeling takes place away from the drying agent region, the protection sheet part of the multilayer laminate can exclusively be peeled off in the product region. This is not possible in the region of the  
35 drying agents since any opening aid such as a seal free zone is lacking.

**Patent claims**

1. Blister package with a pan sheet (4) with preparation cavities (1) and drying agent cavities (2) as well as a cover sheet (5), characterized in that the blister package in the region of the drying agent cavities (2) is reinforced thus, that the withdrawing of the charge with usual finger pressure is prevented, and that the reinforcement over the drying agent cavities (2) can-  
10 not be removed by applying usual means.

2. Blister package according to claim 1, characterized in that at least one preparation cavity (1) is connected with at least one drying agent cavity (2).

3. Blister package according to claim 1 or 2, characterized in that the drying agent cavities (2) are situated adjacently, particularly in one or several adjacent rows.

4. Blister package according to any one of claims 1 to 3, characterized in that the at least one preparation cavity (1) is connected with at least one drying agent cavity (2) by a connecting passage (3).

5. Blister package according to any one of claims 1 to 4, characterized in that the cover sheet (5) comprises an aluminum layer or an aluminum foil, respectively.

6. Blister package according to any one of claims 1 to 5, characterized in that in the region of the drying agent cavities (2) on the cover sheet (5) at least one protection sheet (6) is provided.

30 7. Blister package according to claim 6, characterized in that the protection sheet (6) is a plastic sheet, particularly a PET/PE sheet.

8. Blister package according to claim 6, characterized in that the cover sheet (5) and the protection sheet (6) together form a multilayer laminate and that the multilayer laminate between the preparation cavities (1) and the drying agent cavities (2) is perfo-  
35

rated or sectioned in at least a part of its diameter and in that the blister package has on the preparation side in the region of the perforation or cross section (8) at least one seal free zone (7).

5        9. Blister package according to claim 8, characterized in that the multilayer laminate between the cover sheet (5) and the protection sheet (6) has a layer with restricted laminate adhesion, particularly a lamination adhesive.

10        10. Blister package according to claim 8, characterized in that the cover sheet (5) and the protection sheet (6) are inseparably connected, that the multilayer laminate is peelable as a whole and that the blister besides the perforation or cross section (8) has a  
15        perforation or cross section (9) at least between the preparation cavities (1), preferably between the preparation cavities and between the drying agent cavities.

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Fig. 1

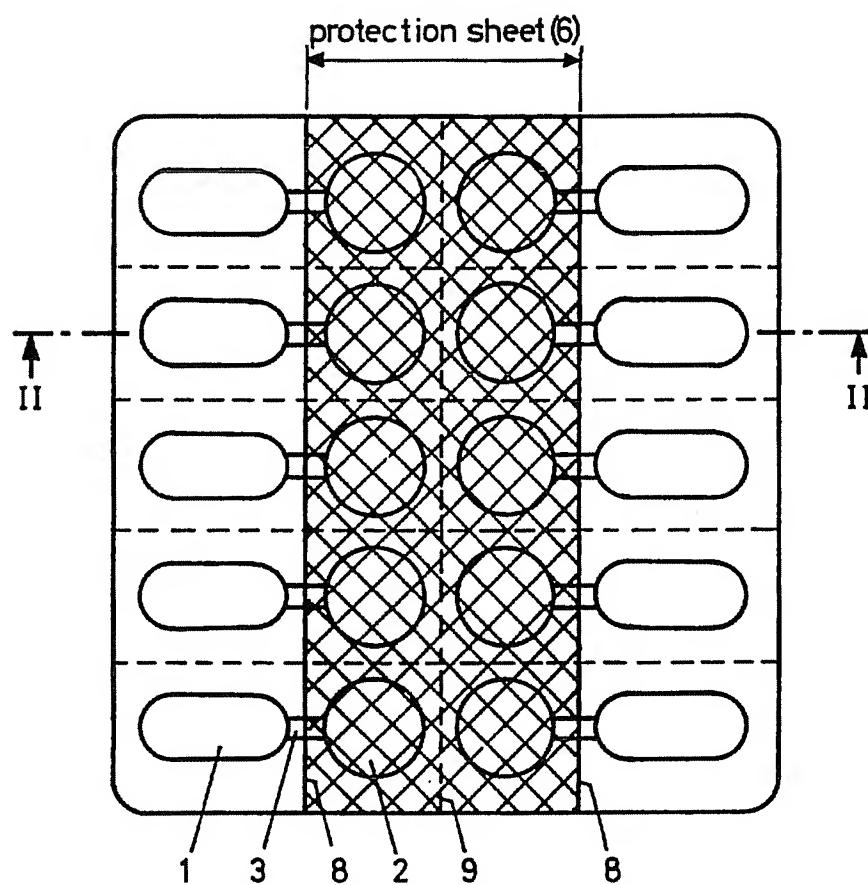
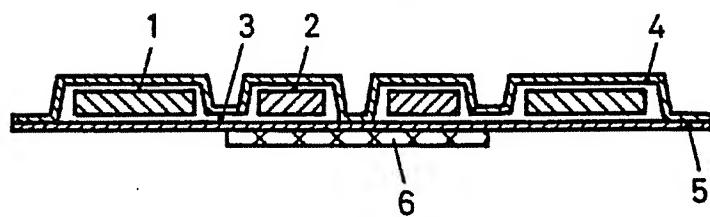


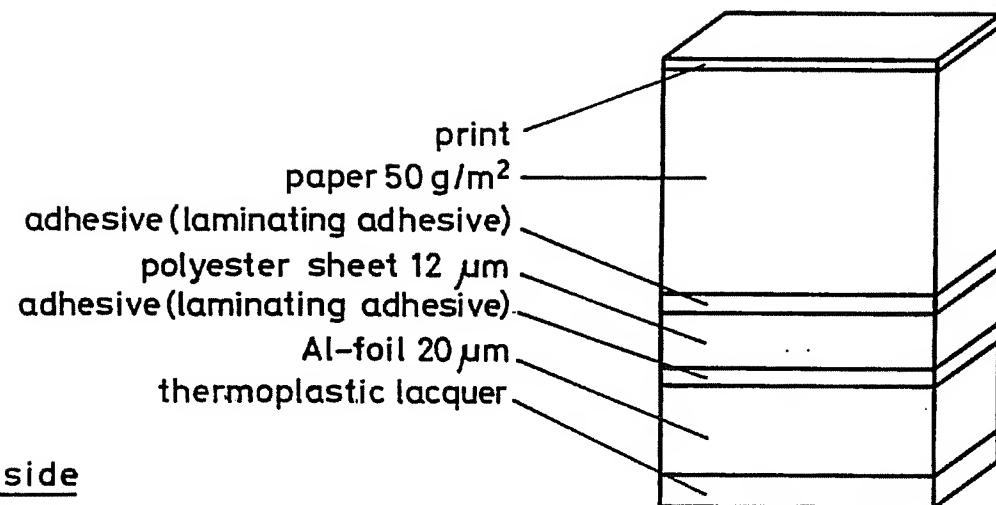
Fig. 2



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Fig. 3

OutsideInside

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Fig. 4

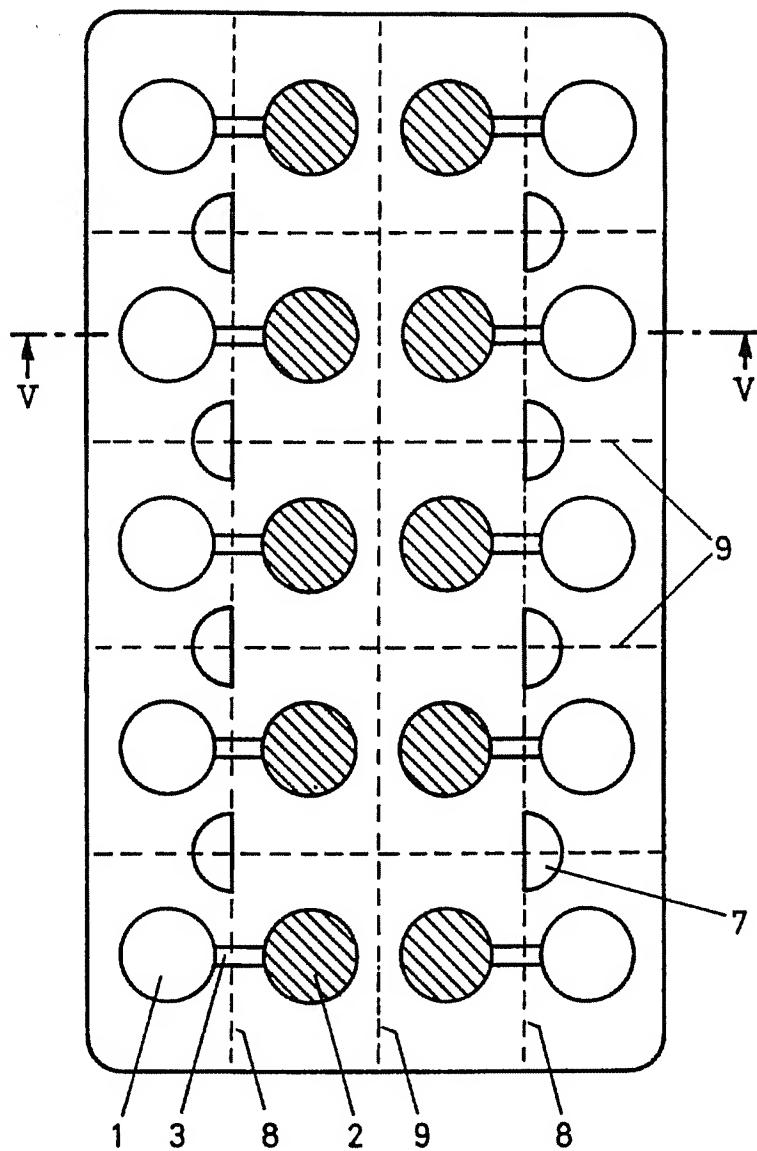
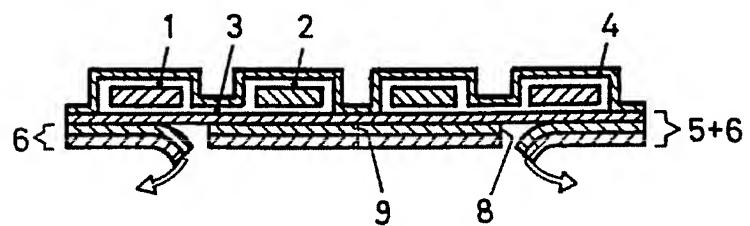
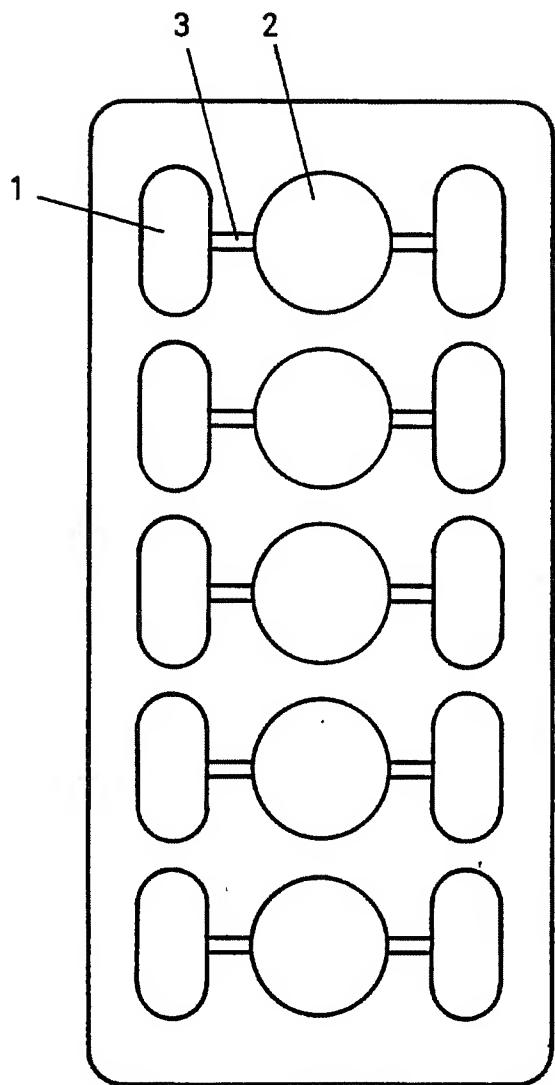


Fig. 5



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Fig. 6



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**INTERNATIONAL SEARCH REPORT**

International Application No

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**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 B65D75/34 B65D81/26

According to International Patent Classification (IPC) or to both national classification and IPC

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	DE,A,24 04 232 (OEHLMANN) 7 August 1975 cited in the application see page 2, line 18 - page 3, line 9 see page 4, line 9 - line 26; figure 1 ---	8-10
Y	DE,A,24 04 232 (OEHLMANN) 7 August 1975 cited in the application see page 2, line 18 - page 3, line 9 see page 4, line 9 - line 26; figure 1 ---	1-7
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Patent family members are listed in annex.

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Date of the actual completion of the international search

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 172 812 (WHARTON) 22 December 1992 cited in the application see column 3, line 34 - line 59; figures ---	6
A	US,A,3 780 856 (BRAVERMAN) 25 December 1973 cited in the application see abstract; figures 1-4,7,10 ---	8
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Information on patent family members

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		JP-A-	49043793	24-04-74
		JP-B-	53040156	25-10-78
		US-A-	3924746	09-12-75